REMARKS/ARGUMENTS

Prior to the present amendments, Claims 49-59 were pending in this application and stood rejected on various grounds. Claims 49-51, 53 and Claim 56 have been canceled without prejudice or disclaimer, merely to expedite prosecution in this case, and Claims 52-54 have been amended. All amendments are fully supported by the specification as originally filed. Specific support for the recitation of "position X of SEQ ID NO:2, wherein X is any amino acid from position 271 to position 280" is at least at page 12, lines 11-23.

Change of correspondence address

A revocation of power of attorney and change of address was filed May 29, 2005 in this case. Accordingly, Applicants respectfully request the Examiner to note the new address:

CUSTOMER NO. 35489
Ginger R. Dreger
HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

Applicants request all future correspondence in this case to be sent to the above mentioned address.

Specification

2 and 4. The specification on page 1 has been amended to reflect the current status of parent U.S. Patent Application Serial Nos. 09/953,499 and 09/254,465 as requested.

3. To address the Examiner's objection under 35 U.S.C. §132 for allegedly introducing new matter, Applicants attach a copy of the transmittal letter accompanying this application as filed under 37 C.F.R. §1.53(b) on January 29, 2004. The transmittal letter clearly recites under Section 1 all applications to which priority is claimed, including U.S. Patent Application Serial Nos. 09/953,499 and 09/254,465, and indicates that "the entire disclosures of [the listed applications] are hereby incorporated by reference." Therefore, the amendments filed on January 29, 2004 or submitted herewith do not introduce new matter.

Accordingly, Applicants believe that all objections to the specification have been overcome and should be withdrawn.

Information Disclosure Statement

5. The Examiner had objected to items 15-17 of the previously submitted IDS because these entries did not comply with the requirements of 37 C.F.R. §1.98(a)(2). Applicants submit that the individual sequence references of the BLAST results provided in items 15-17 were already itemized, providing the accession number, database, author, date of submission or publication, in the IDS submitted April 19, 2004. The Blast results in items 15-17 were merely provided for the Examiner's reference. Accordingly, the Sequence Listing of record, which has been considered by the Examiner, is believed to be both accurate and complete.

Claim Rejections – 35 U.S.C. §112, First Paragraph - Enablement

8. Claims 49-54, 56 and 58-59 were rejected under 35 U.S.C. §112, first paragraph, because "the specification, while being enabling for an isolated polypeptide molecule having the amino acid sequence of the polypeptide of SEQ ID NO:2 to stimulate the proliferation of T-lymphocytes, does not reasonably provide enablement for an isolated polypeptide molecule having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO: 2.....The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim." For the reasons outlined below, Applicants respectfully disagree.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation.[1,2] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is

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[1] M.P.E.P. §2164.01.

[2] *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[4, 5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims. "How a teaching is set forth, by specific example or broad terminology, is not important."[6, 7] "Limitations and examples in the specification do not generally limit what is covered by the claims " M.P.E.P. §2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

It is well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed (emphasis added).[8]

Proper Application of the Legal Test

Claims 49-51, 53 and Claim 56 have been canceled without prejudice or disclaimer, therefore their rejection is moot. The rejection of the remaining claims is respectfully traversed.

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[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[5] M.P.E.P. §2164.06.

[6] M.P.E..P. §2164.08.

[7] *In re Marzocchi*, 439 F.2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

[8] *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Claim 52 is directed to a genus of polypeptides which are at least 95% identical to the amino acid sequence of the polypeptide of SEQ ID NO:2, or the sequence of amino acid position 1 to amino acid position X of SEQ ID NO:2, wherein X is any amino acid from position 271 to position 280, or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209620, and which have a specific and useful function (*i.e.* the ability to stimulate the proliferation of T-lymphocytes).

Claim 54 is directed to an isolated polypeptide molecule comprising the amino acid sequence of the polypeptide of SEQ ID NO:2, the extracellular domain of the polypeptide of SEQ ID NO:2 (between positions 1 and 271-280), or the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209620.

The rest of the claims pending depend from and carry the limitations of one of Claim 52 or Claim 54.

Applicants respectfully submit that all claims pending satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

1) Starting with Claim 54, this claim is directed to polypeptides comprising amino acid sequences which have been disclosed in the specification or otherwise made available to the public (*i.e.*, by ATCC deposit) at the effective filing date of the present application. Accordingly, the Examiner is respectfully requested to withdraw the rejection of Claim 54 and Claims 55 and 57 dependent thereon and carrying its recitations. Indeed, claims were only objected to as being dependent upon a rejected base claim but were indicated as allowable as rewritten in independent form including all limitations of the base claim and any intervening claims. It is submitted that Claim 54, as currently amended, is clearly allowable, therefore, Claims 55 and 57 should also be allowable in their current dependent form.

2) The claimed genus of Claims 52 is directed to polypeptides characterized by a combination of structural and functional features and are based closely on the disclosure provided in the specification.

The Examiner alleges, based on the teachings of Atwood and Skolnick, that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity

between sequences....the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins.....Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm **the artisan's best guess as to the function of the structurally related protein**...even single amino acid differences can result in drastically altered functions between two proteins. Thus, it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences" (emphasis added; see page 3 of instant Office Action).

Applicants respectfully disagree. First of all, Applicants do not make "functional assignments based on sequence similarity" in this instance. Nor do the Applicants' *guess* or require the skilled artisan *to guess* the function of the structurally related protein (a variant PRO362, in this instance). Instead, Applicants clearly teach making and identifying PRO362 sequence variants and testing of these variants in the functional mixed lymphocyte reaction (MLR) assay (well-described in Example 5), without undue experimentation. Therefore, this rejection, based on the teachings of Attwood and Skolnick, is improper, because no prediction or guessing of function for variant PRO362 sequences is needed to practice the instant invention within the full scope of the claims currently pending.

Even though the degree of unpredictability in recombinant DNA technology and molecular biology is admittedly high, based on the teaching of the specification, a person skilled in the art would have had more than enough guidance to make and use the claimed polypeptides.

The specification provides the sequence of the native sequence PRO362 polypeptide, and describes methods of making polypeptide variants (see page 20, line 1 onwards) along with tools for determining the percent identity between two amino acid sequences (see pages 13, lines 3-12). Accordingly, one of ordinary skill in the art, based on the disclosure provided in the specification and general knowledge in the art at the time the invention was made, can readily make a PRO362 variant and determine whether the variant falls structurally within the scope of Claims 52 and 53. Once it has been determined that a sequence is structurally within the scope of these claims, a skilled artisan is able to determine whether any given variant possesses the

ability to stimulate the proliferation of T-lymphocytes, using the assay described in Example 5, which was also well known in the art at the time the invention was made. While some experimentation might be necessary to determine if a particular PRO362 variant is within the scope of the claims pending, as discussed above under the Legal Standard, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that there is nothing in the Examiner's arguments or otherwise of record that would indicate that more than routine experimentation would be required to make and use the polypeptides claimed. Indeed, patents with claims allowing 5% variation within a wild-type sequence routinely issue, *i.e.,* absent some specific scientific evidence of greater than normal degree of unpredictability for a particular polypeptide, such claims are consistently viewed as complying with the enablement requirement of 35 U.S.C. §112, first paragraph. This is clearly supported by the issuance of U.S. Patent No. 6,838,554 on a parent of the present application, which claims nucleic acid molecules having at least 95% sequence identity to a nucleotide sequence encoding a polypeptide of PRO362 or its extracellular domain.

3) Claims 49-54 and 56 were additionally rejected under 35 U.S.C. §112, first paragraph, for reciting a polypeptide molecule that is "lacking its associated signal peptide."

Applicants have removed references to the above mentioned term in the pending claims and have canceled Claim 56, which obviates this rejection.

4) Claims 58 was rejected under 35 U.S.C. §112, first paragraph, for reciting "a heterologous polypeptide." While the Examiner acknowledges that the specification lists "an epitope tag" and "an Fc region of an immunoglobulin" the Examiner asserts that the specification fails to disclose other heterologous polypeptides that can be fused to the claimed polypeptide and at the same time would maintain the structure and function of polypeptide of SEQ ID NO:2.

Applicants respectfully submit that the specification is addressed to one of ordinary skill, who is presumed to be in the possession of all information available in the pertinent art at the time the invention was made. "Heterologous polypeptide" is a term of the art, and one skilled in the art would not only understand what it means but could also readily list heterologous polypeptides, other than epitope tags or immunoglobulin Fc regions, that can be fused to the base sequences recited in the claims pending, without compromising the structural or functional

integrity of the base sequence. Thus, it was well known in the art at the time the present invention was made that polypeptides can be secreted from certain hosts using heterologous signal sequences, or expressed as fusion proteins, such as N- or C-terminal sequences that improve stability, or facilitate purification. Techniques using such heterologous polypeptides were routine in the art at the time of making the present invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claim 58 on this ground.

Claim Rejections - 35 U.S.C. §112, First Paragraph - Written Description

9. Claims 54, 56 and 58-59 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

While the Examiner acknowledges that "the Applicant is in possession of an isolated polypeptide molecule having the amino acid sequence of the polypeptide of SEQ ID NO:2 to stimulate the proliferation of T-lymphocytes," the Examiner alleges that Applicant "was not in possession of an isolated polypeptide molecule having the amino acid sequence of the polypeptide of SEQ ID NO:2, lacking its associated signal peptide in Claims 54 and 56 or a 'chimeric polypeptide' comprising a polypeptide molecule of Claim 54 fused to a 'heterologous polypeptide' in Claim 58". Applicants respectfully traverse this rejection.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[9, 10] The adequacy of written description support is a factual

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[9] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[10] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

issue and is to be determined on a case-by-case basis.[11] The factual determination in a written description analysis **depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure** (Emphasis added). [12, 13]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[14] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." [15] Further, the hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity, have the capability of understanding the scientific and engineering principles applicable to the pertinent art." (Emphasis added).[16, 17]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Claim 56 and references to polypeptides without the signal sequence have been canceled without prejudice or disclaimer. Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO362 polypeptide of SEQ ID NO:2, and its extracellular domain sequence, and chimeric polypeptides comprising heterologous polypeptide sequences.

Applicants were clearly in possession of the polypeptides claimed in Claim 58 since the "chimeric polypeptide comprising a polypeptide of Claim 54 fused to a heterologous polypeptide" is clearly taught at least at page 15, line 20 (chimeric polypeptides) and at least at pages page 22, lines 3-23 (heterologous polypeptides). Thus, based on the "nature of the

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[11] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[12] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[13] *See also* M.P.E.P. §2163 II(A).

[14] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[15] *See also* M.P.E.P. §2141.03.

[16] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[17] S*ee also* M.P.E.P. §2141.03.

invention and the amount of knowledge imparted to those skilled in the art by the disclosure," the 'person having ordinary skill in the art' would "have the capability of understanding the scientific and engineering principles applicable to the pertinent art." The claims clearly meet the written description requirement which requires that an applicant's specification must convey with reasonable clarity **to those skilled in the art** that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) (Emphasis added). Hence, Applicants request that the present rejection to the present claims be reconsidered and withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1216 R1C1D1**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 11, 2005

By: _____
Ginger R. Dreger (Reg. No. 33,055)

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